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Effects of inspiratory impedance on hemodynamic responses to a squat–stand test in human volunteers: implications for treatment of orthostatic hypotension

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Abstract Recent studies in our laboratory demonstrated that spontaneous breathing through an inspiratory impedance threshold device (ITD) increased heart rate (HR), stroke volume (SV), cardiac output (Q), and mean arterial blood pressure (MAP) in supine human subjects. In this study, we tested the effectiveness of an ITD as a countermeasure against development of orthostatic hypotension, provoked using a squat-to-stand test (SST). Using a prospective, randomized blinded protocol, 18 healthy, normotensive volunteers (9 males, 9 females) completed two-counterbalanced 6-min SST protocols with and without (sham) an ITD set to open at 0.7 kPa (7-cm H_2O) pressure. HR, SV, Q, total peripheral resistance (TPR), and MAP were assessed noninvasively with infrared finger photoplethysmography. Symptoms were recorded on a 5-point scale (1 = normal; 5 = faint) of subject perceived rating (SPR). The reduction in TPR produced by SST (-35 ± 5 %) was not affected by the ITD. Reduction in MAP with ITD during the transient phase of the SST (-3.6 ± 0.5 kPa or -27 ± 4 mmHg) was less ($P = 0.03$) than that measured while breathing through a sham device (-4.8 ± 0.4 kPa or -36 ± 3 mmHg) despite similar ($P < 0.926$) elevations in HR of 15 ± 2 bpm. SV ($+2 \pm 4$ %) and Q ($+22 \pm 5$%) with the ITD were higher ($P < 0.04$) than SV (-8 ± 4%) and Q ($+10 \pm 6$ %) without the ITD. SPR was 1.4 ± 0.1 with ITD compared to 2.0 ± 0.2 with the sham device ($P < 0.04$). This reduction in orthostatic symptoms with application of an ITD during the SST was associated with higher MAP, SV and Q. Our results demonstrate the potential application of an ITD as a countermeasure against orthostatic hypotension.

Keywords Respiration · Blood pressure · Heart rate · Stroke volume · Cardiac output · Peripheral vascular resistance

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Introduction

Orthostatic hypotension and frank syncope have proven to be debilitating for military personnel, astronauts returning from space, and patients who suffer from clinical autonomic dysfunctions or prolonged restrictive bed rest (Convertino 1999; Convertino 2002; Grubb et al. 2003; Low et al. 1995). One of the challenges to effective treatment of orthostatic intolerance is maintenance of venous return and stroke volume, particularly in the presence of reduced circulatory blood volume (Convertino 1999; Convertino 2002; Convertino and Cooke 2002; Kimberly and Shoemaker 2002; Shoemaker et al. 1999). Greater negative intrathoracic pressure has been associated with elevations in stroke volume, cardiac output, systemic arterial blood pressure, and organ blood flows in humans and animals (Convertino et al. 2004c; Lurie et al. 1995, 1998, 2000a, b, 2001, 2002a, b;

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Plaisance et al. 2000). Building on this concept, we hypothesized that an inspiratory impedance threshold device (ITD) designed to create a vacuum within the thorax each time the chest expands during inspiration would minimize or eliminate orthostatic hypotension and symptoms that occur when individuals stand up. If our hypothesis proved correct, an ITD could provide a simple therapeutic countermeasure that could be used by individuals who are at risk for experiencing orthostatic intolerance.

Methods

Subjects

Eighteen healthy, normotensive, nonsmoking men and women served as subjects (Table 1). A complete medical history and physical examination that included a resting 12-Lead ECG and clinical orthostatic exam (supine/seated/standing consecutive blood pressure measurements) were obtained on each of the potential subjects. Subjects were refrained from any exercise and stimulants such as caffeine and other nonprescription drugs, 24 h prior to testing. During an orientation period that preceded each experiment, all subjects were made familiar with the laboratory, the protocol, and the procedures. Experimental procedures and protocols were reviewed and approved by the Institutional Review Board of the Kennedy Space Center for the use of human subjects. Each subject gave written informed voluntary consent to participate in the experiments.

Protocol

Each subject completed two squat–stand tests (SST): (a) during spontaneous breathing through a face mask with an active ITD (Advanced Circulatory Systems Inc., Eden Prairie, Minnesota) set at approximately −0.7 kPa (−7 cm H_2O) resistance; and (b) during a control session (breathing through the same face mask with a sham ITD). An ITD includes a specially designed valve that closes when the pressure within the thorax is less than atmospheric pressure and a second valve (termed the safety check valve) that opens at a preset negative intrathoracic pressure (Fig. 1a). The ITD is comprised of the valve attached to a facemask to ensure that a seal existed sufficient to eliminate any air leakage between the valve and the skin of the subjects' face (Fig. 1b). An ITD set with a −7 cm H_2O cracking pressure at a flow rate of 20 l min^{-1} (i.e., the pressure at which the valve opened, allowing air inflow) was chosen because this impedance level was previously proven to be tolerable and increase arterial blood pressure, heart rate, stroke volume, and cardiac output in human subjects (Convertino et al. 2004b; Convertino et al. 2004c). There is little resistance during exhalation. Each subject had his/her own disposable face mask. The order of treatment was counterbalanced with a computer-generated randomization list so that 9 subjects (5 males and 4 females) underwent orthostatic testing during active ITD treatment first while the remaining 9 subjects (4 males and 5 females) underwent testing with the sham ITD treatment (control condition) first. During the SST, subjects were instructed to hold the ITD in place with the right hand and assume a squatting position as deeply as possible while maintaining adequate balance without touching the floor with their hands for a 4-min time period (Fig. 2a). Fifteen seconds prior to standing, each subject was instructed to start breathing through the ITD mask with natural but deep breaths. At the 4-min mark of squatting, each subject was instructed to stand erect as quickly as possible without using their hands to assist them and continue standing for 2 min (Fig. 2b). They were instructed to breath continuously through the ITD from 15 s prior to standing until 2 min after standing. Measurements of arterial blood pressures, heart rate, and stroke volume were collected continuously throughout each SST and stored on a data acquisition system based in Labview. Cardiac output and total peripheral resistance were calculated from mean arterial blood pressure, heart rate, and stroke volume. These key hemodynamic measurements that reflected the changes in position from squatting to standing were made by beat-to-beat analysis during the 10-s period of time starting immediately upon standing after four minutes of squatting. The subjects provided an indication of their perceived rating of orthostatic stress during the transition from squat to stand positions. A minimum of 30 min intervened between each SST so that each experimental session was conducted over a period of less than 60 min.

Table 1 Subject group demographic data

	Females ($n=9$)	Males ($n=9$)
Age, yr	32 ± 3	36 ± 4
Height, cm	163 ± 2	179 ± 1
Weight, kg	54.6 ± 2.6	84.0 ± 2.6
Heart rate, bpm	65 ± 5	62 ± 3
Systolic blood pressure, mmHg	124 ± 6	130 ± 4
Diastolic blood pressure, mmHg	67 ± 5	68 ± 3

Values are mean ± 1 standard error

Hemodynamic measurements

Continuous heart rate (HR) was measured from a standard electrocardiogram. Real-time beat-to-beat continuous estimates of arterial systolic (SBP) and diastolic (DBP) blood pressures were measured noninvasively using infrared finger plethysmography (IFP) with a Portapres Blood Pressure Monitor (TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands). The Portapres blood pressure cuff was placed on the middle finger of the left hand which, in turn, was held to the chest

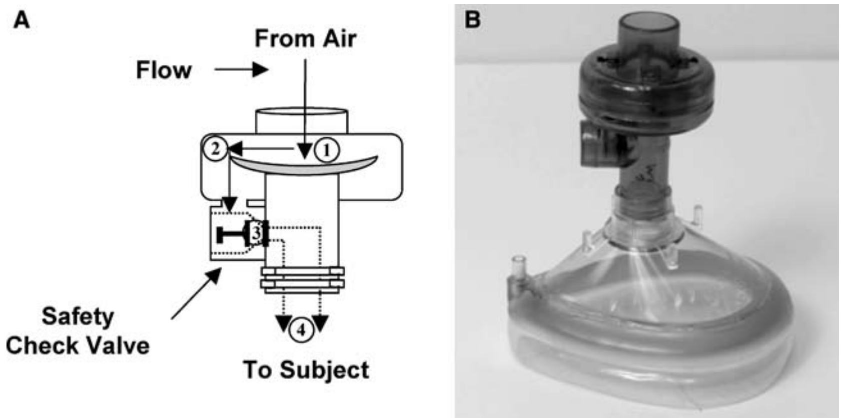

Fig. 1 *Left panel* (**a**) is a drawing illustration of the impedance threshold valve. During spontaneous inspiration, air flow from the ventilation port to the subject causes a silicone diaphragm to close (Step #1). The air flow bypasses the diaphragm to the safety check valve (Step #2). When intrathoracic pressure exceeds the imped ance threshold of the valve, the safety check valve opens (Step #3) and air reaches the subject (Step #4). *Right panel* (**b**) is a photograph of the impedance threshold device (ITD) consisting of the valve attached to a mask

at heart level. Excellent estimates of directly measured intraarterial pressures during Valsalva maneuvers have been demonstrated with this device (Imholz et al. 1988). Mean arterial pressure (MAP) was calculated by dividing the sum of SBP and twice DBP by three.

Beat-to-beat stroke volume (SV) was estimated non-invasively from changes in pulse waveforms measured by application of IFP with the Portapres. Stroke volume estimation by application of IFP is based on the computed aortic flow pulsations from arterial pressure waveforms by simulating a nonlinear, time-varying three-element model (aortic characteristic impedance, arterial compliance, and systemic vascular resistance) of aortic input impedance (Wesseling et al. 1993). Comparisons of 76 cardiac output measures using IFP during open-heart bypass surgery in eight patients produced a mean deviation of ±2% (with SD of 8%) when compared to 76 simultaneous thermodilution measurements (Wesseling et al. 1993). Cardiac output (Q) was calculated as the product of HR and SV. Total systemic peripheral resistance (TPR) was calculated by dividing MAP by Q, and is expressed as peripheral resistance units.

Subject perception rating of orthostatic stress

Each subject was instructed to verbally provide a SPR of orthostatic symptoms (lightheadedness and presyncope) based on the following 5-point scale: 1 = normal; 2 = mild; 3 = moderate; 4 = severe; 5 = faint. The SPR score was provided immediately upon assuming the standing posture and following 1 min after standing.

Statistical analysis

We performed a standard 2 group (male, female) by 2 treatment (−7 cm H_20 ITD, control) mixed model analysis of variance to determine gender differences. The model was mixed in the sense that the subjects were nested within gender groups and were crossed with treatments [i.e., one between subjects factor (gender) and one within subjects factors (treatment)]. All main effects and subsequent interactions were analyzed across six dependent effects (MAP, HR, SV, Q, TPR, SPR). Exact

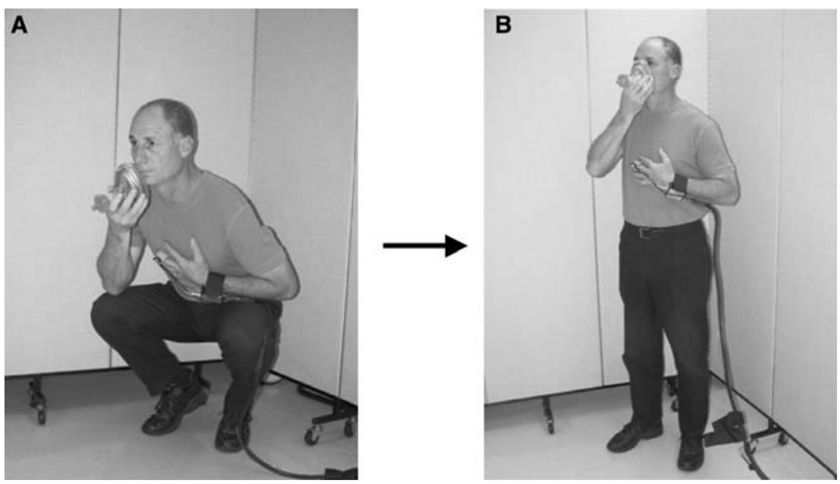

Fig. 2 Photographs of a subject beginning in the squat posture (*left panel* **a**) and progressing to the stand posture (*right panel* **b**)

P values were calculated for each independent effect and these reflect the probability of obtaining the observed or greater effect given only random departure from the assumption of no effects. Standard errors are raw measures of variation about the specific treatment group mean and do not reflect variability specific to the factors being tested or the variability associated with statistical tests and subsequent P values given in the text.

Results

Demographic data

There were no statistically distinguishable differences between gender groups for age, heart rate and blood pressures. Gender groups showed the expected and well-established differences on height and weight. Values for heart rates and blood pressures were within established normal limits.

ITD and gender effects

Gender did not influence the responses of MAP ($F=0.348$, $P=0.563$), HR ($F=0.136$, $P=0.718$), SV ($F=1.456$, $P=0.244$), Q ($F=0.384$, $P=0.544$), TPR ($F=0.669$, $P=0.425$), or SPR ($F=0.062$, $P=0.807$) across treatment during either spontaneous breathing through the ITD or control experimental conditions. Consequently, the data were combined and analyzed with t-test statistics as a sample size of 18.

Hemodynamic effects

The change in posture from squat to standing caused similar reductions in total peripheral vascular resistance (-35 ± 5 %; $P=0.768$) and elevations in heart rate (15 ± 2 beats per min; $P=0.926$) with and without inspiratory impedance (Fig. 3). By contrast, SV ($+2\pm4$ %) and Q ($+22\pm5$ %) with the active ITD were higher ($t\geq2.213$, $P \leq 0.04$) than SV (-8 ± 4 %) and Q ($+10\pm6$ %) with the sham ITD (Fig. 4, top panels). Subsequently, the average reduction in MAP of 3.6 ± 0.5 kPa (27 ± 4 mmHg) with spontaneous breathing through the ITD during the move from squat to standing (110 ± 3 to 83 ± 4 mmHg) was less ($P=0.032$) than the decrease of 4.8 ± 0.4 kPa (36 ± 3 mmHg, i.e., 110 ± 4 to 74 ± 4 mmHg) measured while breathing through a sham device (Fig. 4, bottom panel). The SPR was 1.4 ± 0.1 with ITD compared to 2.0 ± 0.2 with the sham device ($P=0.035$) immediately upon standing, but returned to 1.3 ± 0.2 in both ITD conditions by 1 min of standing.

Discussion

One of the primary mechanisms that contribute to orthostatic hypotension and ultimately syncope is the reduction in cardiac filling and SV in the absence of adequate autonomically mediated compensatory responses (Blomqvist and Stone 1982). Based on this premise, a therapeutic approach designed to enhance venous return and SV should act as an effective countermeasure against orthostatic intolerance. The application of resistance during spontaneous inspiration has been shown to cause an immediate increase in arterial blood pressure when applied in different clinical models associated with significant life-threatening hypotension (Lurie et al. 1995, 1998, 2000a, b, 2002a, b ; Plaisance et al. 2000) as well as in normal healthy supine humans (Convertino et al. 2004a, b) and animal models of shock and cardiac arrest (Lurie et al. 2004). The concept by which the ITD functions to increase blood pressure is based on the mechanics of producing a greater vacuum within the thorax during each inspiration, which subsequently draws a larger amount of blood from the extrathoracic venous system into the heart, thereby enhancing cardiac filling (Lurie et al. 2000a, b, 2002a, b). Thus, the ITD functions like a modified Mueller maneuver. We, therefore, hypothesized that the application of respiratory resistance produced by an ITD would result in higher SV, Q, and arterial blood pressure under conditions of a severe orthostatic stress. To test this hypothesis, we measured SV in normovolemic, normotensive human subjects when they breathed through an ITD during the transition from a squatting

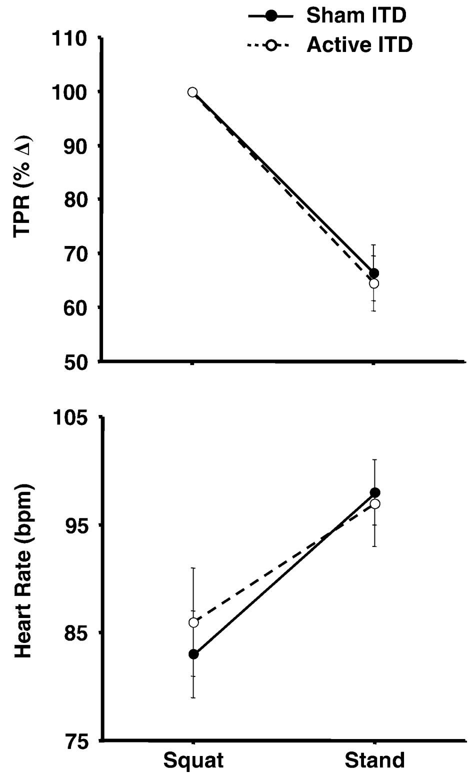

Fig. 3 Changes in total peripheral resistance (TPR) (*panel* **a**) and heart rate (*panel* **b**) during spontaneous breathing on a sham (*closed circles*, *solid lines*) and active (*open circles*, *broken lines*) ITD. *Circles* and *lines* represent mean ± 1 standard error ($n=18$)

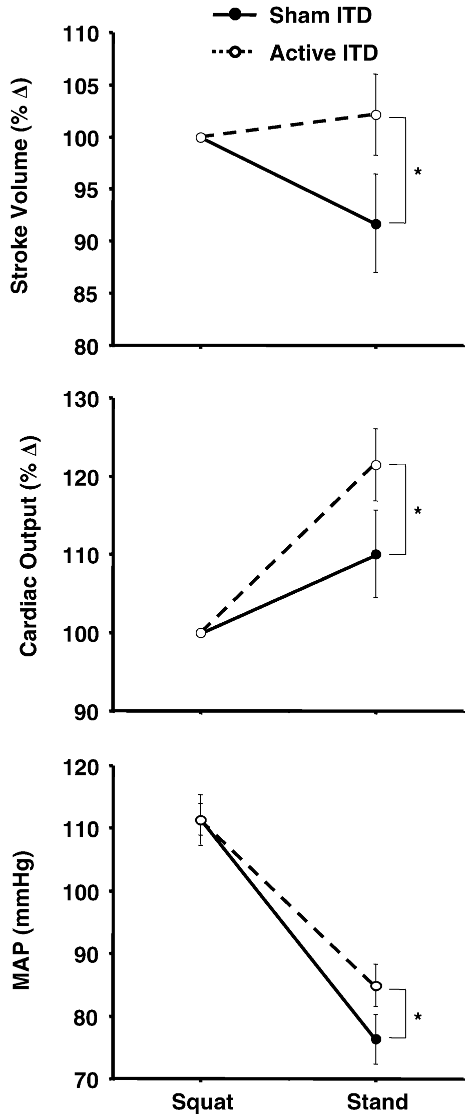

Fig. 4 Changes in stroke volume (*upper panel*), cardiac output (*middle panel*), and mean arterial blood pressure (*lower panel*) during spontaneous breathing on a sham (*closed circles*, *solid lines*) and active (*open circles*, *broken lines*) ITD. *Circles* and *lines* represent mean ± 1 standard error ($n = 18$). *Asterisk* indicates $P < 0.04$

posture to standing. The results confirmed that application of the ITD ameliorated the hypotension caused by the SST by increasing SV and Q.

The inability to elicit adequate peripheral vascular constriction is a common feature of individuals susceptible to orthostatic intolerance (Convertino and Sather 2000; Buckey et al. 1996; Convertino et al. 2004a; Waters et al. 2002). The SST is a unique orthostatic model since it produces an immediate pronounced reduction in total peripheral resistance during the transition from squat to standing (Convertino et al. 1998). Since the initial response of sympathetically mediated peripheral vasoconstriction requires 2–3 s to occur (Eckberg and Sleight 1992) with maximum effect requiring approximately 10–15 s (Convertino et al. 1998), a reactive hyperemia in the lower legs induced by the squat position induces a highly reproducible vasodilation and subsequent reduction in total peripheral resistance during the transient 10 s of standing (Convertino et al. 1998; Fig. 3). In the present study, we used the beat-to-beat measurements of hemodynamic responses during the initial 10-s time interval of standing immediately following 4 min of a squat posture as an orthostatic challenge designed to assess the effectiveness of an ITD on central cardiac function during pronounced hypotension in the absence of reflex compensatory peripheral vasoconstriction. Our results suggest that spontaneous breathing through the ITD can be effective in ameliorating orthostatic symptoms in individuals with impaired peripheral vasoconstriction.

Central venous pressure and cardiac filling are reduced during standing (Blomqvist and Stone 1982). Recent studies have demonstrated that use of an ITD increases left ventricular end-diastolic volume (Lurie et al. 2002b; Samniah et al. 2003) and end-tidal CO_2 (Lurie et al. 2000a, b; Plaisance et al. 2000) in the conditions of low central blood volume in animal models. These observations raise the possibility that a Starling effect with a subsequent increase in SV and Q represents an underlying mechanism associated with the elevated blood pressure during inspiratory resistance (Coast et al. 1988). The ability of the ITD to ameliorate orthostatic hypotension during the squat–stand test in the present study resulted from higher SV and Q compared to the control condition. Although we were unable to measure cardiac filling, our results suggest that the ITD most likely increased cardiac filling and/or myocardial contractility. Cardiac filling can be influenced by increased blood volume, greater filling time, higher preload (central venous pressure), and lower afterload. Since the comparison of the ITD with the control condition was conducted within 60 min, it is unlikely that blood volume was altered. The heart rate response to standing was also similar between the ITD and the sham device, suggesting that cardiac filling time could not explain stroke volume differences between experimental conditions. Since arterial blood pressure was higher during spontaneous breathing through the ITD compared to sham device (i.e., less hypotension), afterload could not explain higher stroke volume in the ITD condition. It, therefore, appears most likely that a primary contributing mechanism by which the ITD increased stroke volume and cardiac output during the initial 10 s of standing was enhanced-cardiac filling and a subsequent increase in myocardial contractility (i.e., a Starling effect). This conclusion is consistent with the observations made when using an ITD in combination with a phrenic nerve stimulator in animals in hypovolemic shock; each inspiration through the ITD was associated with a marked increase in right heart filling (Samniah et al. 2003).

During the transient phase of the squat–stand maneuver, the HR was increased to the same degree with both ITD and sham conditions. Because ITD increased arterial blood pressure, we had anticipated a lower HR response mediated by arterial baroreflex feedback control. Against expectations, ITD breathing elicited an equal tachycardic response in the face of a higher arterial blood pressure. Although this HR response seems contraindicated, our finding corroborates earlier observations of elevated HR with the ITD. The ITD-mediated elevation in HR is similar to the concurrent elevation in HR and arterial blood pressure responses observed during physical exercise in which increased negative intrathoracic pressures are associated with the resetting of the cardiac baroreflex stimulus–response relationship to a higher operating range (Raven et al. 1997; Rowell 1986). We also found that the elevated HR response during ITD breathing was associated with a resetting of the baroreflex to a higher operating range in our subjects (Convertino et al. 2004b). Thus, the increase in cardiac output with less hypotension elicited by spontaneous breathing through the ITD during the transition to standing involves mechanisms that contribute to elevations in both SV and HR.

In addition to effects on cardiac filling and baroreflex function, we cannot dismiss the possible contribution of increased central inspiratory drive (CID) to elevations in blood pressure and HR observed during ITD breathing. Hellstrom et al. (1999) showed that CID (as estimated by the pressure drop during a 0.1 s occlusion at the onset of inspiration) was doubled with inspiratory threshold loading at a level similar to that used in the present investigation (6-cm H_2O). It is, therefore, likely that the tachycardia and relative hypertensive response with ITD breathing resulted in part from an increase in CID at the medullary level that acted in concert with an augmented preload.

Although modest, the difference in the average reduction in MAP of 1.2 kPa (+9 mmHg) at the transition of standing observed in our subjects during ITD breathing compared to the sham device may be important in that it occurred in healthy normovolemic, normotensive subjects. We hypothesize that even larger enhancement of Q and arterial pressure may be produced by spontaneous resistance breathing in individuals with severe hypovolemia (e.g., dehydration, hemorrhage) or patients with clinical autonomic dysfunctions when venous return is compromised. This hypothesis is currently being tested using ITD application in human models of central hypovolemia. In any event, the association of a modest elevation in MAP during breathing through the ITD with the dramatic elimination of orthostatic symptoms may reflect the importance of maintaining a minimal perfusion pressure for adequate cerebral blood perfusion.

Test subjects reported fewer symptoms (e.g., lightheadedness, blurred vision) when breathing through the active ITD. Recently, we have demonstrated that use of the ITD increases cerebral blood flow (Cooke et al. 2005). In previous experiments, we observed a concurrent reduction in intracranial pressures when a negative intrathoracic pressure is generated with the ITD, supportive of an important thoracocranial interaction (Convertino et al. 2005). In the present study, we were unable to assess cerebral blood flow or intracranial pressure during SST. However, we speculate, based upon our other human and animal studies, that inspiration through the ITD decreases both intrathoracic and intracranial pressures during the peak inspiratory effort, thereby enhancing cerebral perfusion pressures, even in the setting of relative hypotension. If this hypothesis is correct, it may help explain why subjects expressed less symptoms associated with orthostatic compromise (e.g., dizziness, faintness) immediately upon standing when inspiring through the active ITD.

Because our subject population was composed of males and females, we had the opportunity to test the hypothesis that the effectiveness of inspiratory resistance would be less in females since women have greater risks of circulatory collapse during acute central hypovolemia than men (Convertino et al. 1998; Convertino 1998). Both male and female subjects in our study demonstrated similar elevations in SV, Q and MAP when breathing through the ITD. Therefore, we conclude that application of an ITD is equally effective for enhancing the hemodynamic mechanisms associated with elevation in blood pressure in a population of subjects who may be at higher risk for circulatory collapse.

In summary, we demonstrated that spontaneous breathing through an ITD (i.e., increased inspiratory resistance) ameliorated orthostatic hypotension in the absence of appropriate peripheral compensation by enhancing Q. The higher Q resulted from greater SV and HR. The increase in systemic blood flow appeared to contribute significantly to maintaining adequate cerebral blood perfusion as indicated by the significant amelioration of subjective symptoms.

Clinical implications

Breathing through the ITD was well tolerated by our subjects. We have reported similar ventilatory mechanics (volume and rate) and oxygen uptake when subjects breathed through either a sham or an active ITD with a cracking or opening pressure of −6 cm H_20 for as long as 14 min (Convertino et al. 2004a, b). The results of this investigation are relevant to the application of the ITD for treatment of orthostatic hypotension. In the absence of adequate autonomically mediated reflex peripheral vasoconstriction, mechanical enhancement of venous return and cardiac filling could provide a compensatory mechanism against the development of syncope for some patients. At the present time there are few clinical therapies, with the exception of chronic use of elastic support stocking, inflatable shock trousers, drugs that cause systemic hypertension (e.g., fludrocortisone, midodrine), or invasive techniques such as intravenous fluids and intravenous vasopressor drugs, which acutely increase Q and blood pressure in states of orthostatic hypotension. The ITD presents numerous functional advantages for clinical application. The ITD effects are immediate and not associated with any known adverse effects. It is FDA-approved for use as a "circulatory enhancer" that is noninvasive, nonpharmacological, and nontethered. The ITD is small (weighs less than 150 g), relatively inexpensive (~100 USD), and is simple to use. The results of the present investigation support the concept that transforming the thorax into a more active vacuum by application of an ITD during an orthostatic stress, particularly in the early stages when sympathetically mediated vasoconstriction may be compromised, can provide an effective therapeutic aid for avoiding the development of orthostatic hypotension and syncope by rapidly restoring central blood volume, Q, and blood pressure.

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